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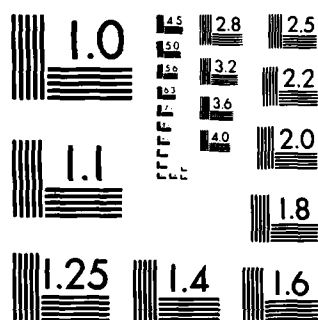
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Annual Progress Report

June 1977

(1 September, 1976- June 1977)

Edward Balish, Ph.D.

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Many fungi are capable of causing serious and even fatal infections in normal individuals and in debilitated patients. The problem is especially serious with patients undergoing cytotoxic, immunosuppressive or broad spectrum antibiotic therapy. Fungal infections cause a large loss of man hours for the U.S. Army, their treatment is poor, prolonged, and they are difficult to eradicate completely. This is expecially true for the dermatophytes.

Suppression of in vitro Blastogenesis by Trichophyton mentagrophytes.

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20. (Continued)

Experimental primary dermatophyte infections of guinea pigs are subacute, usually resolving in 3 to 4 weeks. Experiments were designed to correlate in vitro lymphocyte transformation with fungal growth and elimination from the skin. An inverse relationship between mitogenic activity and the number of viable skin fungi was observed. Hartley Strain II guinea pigs were shaved and cutaneously infected on the back with a mycelial culture of T. mentagrophytes (ATCC 18748). Groups of animals were sacrificed at weekly intervals. Samples of infected skin (cm^2) were ground and plated for fungal enumeration. Colony forming units increased during the first two weeks after infection and then decreased as the lesion cleared. Spleen and lymph node lymphocytes were cultured in vitro with mitogens and specific dermatophyte antigens. Mitogenic activity decreased markedly over the first two weeks of infection and then returned toward normal during lesion resolution. Dermatophyte antigen specific blastogenesis was not observed until day 21, and only in lymph node lymphocyte cultures. These results suggest a compartmentalized depletion of reactive lymphocytes from lymphoid organs during early infection and repopulation during resolution.

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Progress Report
(1 Sept. 1976-June 1977)

Introduction

Germ-free animals are a unique animal model for studies on infectivity, pathogenesis, acquired immunity, prophylaxis, and therapy of dermatophyte infections because: 1) there are no skin or gut bacteria to augment (or hinder) the true course of an experimental dermatophyte infection, 2) germ-free animals have not had any previous exposure to viable dermatophytes and thus the problem of contending with immunological effects from prior subclinical fungal infections is eliminated, 3) true immune responses (both antibody, AMI, and thymus-dependent cell-mediated immunity, CMI) can be assessed without competition and/or antigenic stimulation by the viable bacteria and other fungi that are so prevalent in, and on, experimental animals, 4) when activated, the antibody and cell mediated immune responses of the germ-free animal are every bit as good as, and in some instances better than, the conventional animal; therfore, an assessment of pure primary induction of CMI and AMI occurs. Therapy (either topical or systemic, i.e. steriods or Griseofulvin) on the dermatophyte infection can be assessed without interference from competing bacteria, or previous subclinical dermatophyte infections, 6) the effect of skin microorganisms or their inhibitory products, on the course of dermatophyte infections, can be evaluated in the gnotobiotic model (7). Cellular infiltrates of truely primary skin test responses can be assessed in gnotobiotic animals (8). Germ-free nude mice can be used to study the early stages of dermatophyte growth and infectivity on the skin in a bacteria-free or defined-microbial environment.

It is now known that T. mentagrophytes and other dermatophytes, when looked for, can be isolated from all conventional guinea pig, rat, and mouse colonies (5). This limits the usefulness of conventional guinea pigs, rats, and mice in studies on immunity, prophylaxis and therapy of dermatophyte infections.

Our research program is using germ-free rats, guinea pigs, and nude mice as models for dermatophyte infections. We have studied dermatophyte infections in conventional rats, guinea pigs and flora defined nude mice (i.e. an animal without a functional T-cell capability). Our results with each of these animal models will not be detailed.

Microorganisms: Our studies have been carried out with Trichophyton mentagrophytes; work on C. albicans, used in some of these studies is supported by a grant from the Research Corporation (Minneapolis, Minn.) and by an NIH training grant (AI-0045-04).

General Comments

Germ-free and Conventional Guinea Pigs: Our infections of conventional guinea pigs (Hartley strain and strain 2) have manifested the gross pattern of dermatophyte infection already described by the LAIR group (Akers, Kerbs, Jones, et al) for conventional guinea pigs. Our only information to add to their conventional system is in the area of the cellular infiltration (histology) of lesions and skin tests and on lymphocyte blastogenesis assays. We are seeing much more Eosinophil and Neutrophil involvement in lesions and skin tests (on conventional guinea pigs)

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than one would normally expect in a classical PPD delayed type hypersensitivity response. Collaboration with Drs. Kerbs and Lancaster (LAIR) on the skin tests responses (histology) of germfree and monoassociated guinea pigs to purified dermatophyte antigen will surely help to clarify basic questions on the best antigen to use for skin testing, blastogenesis and possibly, immunization. Also, we will be able to ascertain whether different antigens evoke different skin test responses in the animals, i.e. Jones-Mote type of reaction or the classic PPD type of delayed response with monocytes.

Randomly bred strain 2 guinea pigs (i.e., the conventional controls of germfree guinea pigs used in this study) were shaved (on the back) and inoculated with a 2-4 week old mycelial phase culture of T. mentagrophytes that was grown on Sabourauds' agar. No occlusive dressings were applied. The temporal course of infection is shown in Table 1. Groups of animals were sacrificed at weekly intervals beginning with day 0 and squares of infected lesion (skin) were excised (3/animal) and ground (in glass tissue grinders) and plated out (10 fold dilutions) in order to enumerate colony forming units of T. mentagrophytes, (CFU's). Irrespective of inoculating dose (10^2 or 10^4) figure 1 shows that colony forming units peaked between days 7-14 and then decreased. This decrease in CFU's correlated with the gross resolution and clearance of the lesion (Fig. 2). See Materials and Methods for methodology on skin CFU's.

Lymphocyte transformation

Spleens and a pool of lymph nodes (cervical-tracheal, axillary and supra-scapular) were excised from these same animals (3 animals at each sacrifice). Tissues were minced and pushed through 60-mesh stainless-steel wire screens; washed 3X in PBS; resuspended in RPMI and diluted to give a concentration of 1-2 x 10^5 cells/well (microtiter plates) with 5% homologous (heated) guinea pig serum. Various concentrations of antigens (10-50 µg) and mitogen (1-50 µg) are added to lymphocytes on day 0. Cultures are then incubated for 96 hours at which time 2u curies of ^{3}H-thymidine are added to each well of a microtiter plate. Lymphocytes from each well of the microtiter plate are precipitated on fiberglass filters and counted for radioactivity. Stimulation indices for each mitogen or antigen were calculated by dividing:

$$\frac{\text{cpm stimulated}}{\text{cpm controls}} = \text{S.I. stimulation index}$$

Table II shows the blastogenic response of splenocytes from T. mentagrophytes infected guinea pigs. The capacity of splenocytes to respond to mitogens (ConA and PHA) decreased markedly over the first 14 days of the dermatophyte infection and then started to return to normal on day 21. No positive splenocyte blastogenesis was observed with T. mentagrophytes antigens during the first 21 days.

Table III shows the blastogenic response of regional (to lesion) lymph node lymphocytes. Contrary to splenocytes, a much improved response of lymph node lymphocytes was observed with ConA and PHA on day 21 and a response to dermatophyte antigen was observed at that same time. The

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suppressive effect with mitogens, during the first 14 days after infection, was still observed, however.

In figure 2 we have graphically illustrated the antigenic load of T. mentagrophytes on the skin (as detected by counting CFU's of homogenized-infected skin) and demonstrated how, as the fungal load increased blastogenesis to polyclonal mitogens decreased; to a maximum of 90% on day 14. The blastogenesis began to increase and response to dermatophyte antigen was evident as the fungal load was diminished.

These are most interesting observations that have not been made previously on dermatophyte infections. A better understanding of this suppressive process and the mechanism of suppression could result in some basic new information on chronic dermatophyte infections.

Germfree Guinea Pigs: We have now for the first time infected germfree guinea pigs with T. mentagrophytes. The overall infection rate was 100%. The infection and host response seems to be more severe and persistent (no regrowth of hair and still obvious, open, serous lesions at 50 days past infection in 1 of 4 guinea pigs). The infection does not spread beyond the original site of inoculation and no obvious fungal overgrowth occurs in the germfree isolator. There was no apparent colonization of the nasal cavity, oral cavity or rectal area of the bacteria free guinea pigs. We allowed the infected animals (primary) to continue on in order to see how long it took for the lesion to clear and hair to grow back in the monoassociated (gnotobiotic) state. The hair grew back on all animals in 85 days. Almost 2½ times as long as comparable conventional controls.

This germfree model will be an excellent one for studying therapy and prophylaxis because of its chronic persistent nature. Also, it is very obvious that prior immunological experiences (the microbial flora) of conventional guinea pigs does reduce the severity and duration of dermatophyte infections in the conventional state. The lesions on conventional guinea pigs are not as severe or as prolonged as we have observed in the germfree guinea pig model.

Studies on skin tests, blastogenesis, humoral responses (i.e. antibody production) are now and will continue to be in progress on the germfree guinea pigs while the initial observations on temporal aspects of infectivity, primary and secondary, are being completed.

To date we have seen that a secondary infection in the T. mentagrophytes gnotobiotic guinea pig runs a course very similar to the course observed in a primary infection of conventional animals. Thus, prior experience with a dermatophyte in the absence of other microorganisms does shorten the duration and severity of the secondary infection (acquired immunity?). Monoassociated guinea pigs do respond to the polyclonal mitogen (PHA, Con A, Pokeweed mitogen) and to specific dermatophyte antigens. There is also a positive delayed hypersensitivity skin test (to purified T. mentagrophytes antigen) in the gnotobiotic guinea pigs that have cleared a primary infection. Histology of lesions, skin tests, and temporal fungal load and blastogenesis are still being studied.

Our future plans for the germfree guinea pigs are to see if there is a suppression of polyclonal mitogen lymphocyte response following a primary or secondary infection with T. mentagrophytes and to reinforce our observations on the temporal aspects of primary and secondary infections in the germfree state. Specificity of resistance, skin test histology to purified antigens, elaborating the class of antibody produced in the primary infection and assessing the response of lymphocytes to various purified antigens (from LAIR) are all planned for our studies in the future.

Studies with germ-free and conventional rats: Can dermatophytes, by themselves, infect rats that are free of a viable bacterial and fungal flora? To date our results indicate that germfree rats (and guinea pigs) can be infected by a pure culture of dermatophyte. Obvious infectious lesions, were observed in germ-free and conventional rats, challenged with T. mentagrophytes. We were unable to cause any obvious dermatophyte lesions with Microsporum canis or with Epidermophyton floccosum in the germfree rats. It is also worth noting that none of the 3 fungi used i.e. E. floccosum, M. canis, or T. mentagrophytes was able to colonize the bacteria free GI tract, oral cavity, nasal cavity or lungs of the germfree rats: only T. mentagrophytes was found in low numbers (10^2 - 10^4 gm of the feces from cecum and colon only). This is most interesting because even in the absence of competing bacteria, these fungi do not colonize or invade mucosal epithelial cells or keratinized stomach epithelium. Conversely, the germfree rat does show invasive hyphae in the keratinized portion of their stomach after monoassociation with C. albicans (22).

Another interesting aspect of the germfree rat model is that T. mentagrophytes infects (hyphae invade epidermis) the skin at the inoculated site. None of the germfree rats showed any lesions other than at the site of inoculation and only erythema was evident. No fungal overgrowth occurred in the chambers or on the animals skin at sites other than those experimentally infected. The T. mentagrophytes lesion (a red erythema) in germfree rats clears in 14 days. The lesion is not as severe as we observed in the guinea pig since it clears (erythema) sooner in the germfree rat (14 days) and hair grows back by 30 days. Conversely, conventional rats infected with T. mentagrophytes had scaly skin and no hair growth occurred at the inoculated site for 60-70 days.

The chronic T. mentagrophytes infection that persisted for 60-70 days in conventional rats is of interest because it was a low grade infection and not an ulcerating lesion like we see in guinea pigs. This conventional rat model could be very useful for trials in topical or systemic therapy of fungal infections. The only visible evidence of dermatophyte infection was scaly skin and a lack of hair growth for 60-70 days. Fungi did pentrate and persist in the stratum corneum of the rat.

To date our studies have shown that skin from T. mentagrophytes lesion sites, in the conventional rat only, have a histopathological picture similar to psoriasis. This is a most interesting aspect of the work and it may indicate that a dermatophyte infection may be a mechanism for triggering psoriasis. Since it did not occur in the germfree state however, it may indicate that skin bacteria are involved in its etiology. These experiments on rats also demonstrate that conventional rats can carry T. mentagrophytes on their skin, without overt indications of dermatophyte infection, for prolonged time periods; culture and histology and no growth of hair were the only indications of a gross abnormality to the rats skin.

It should be remembered that in Vietnam, rats appeared to be an important vector for T. mentagrophytes. We have shown that rats have a capacity to carry T. mentaprophytes subclinically on the skin and in the GI tract for at least 70 days (termination of our experiment).

A significant stimulation of peyers patches was also observed in the small intestine of germfree rats infected with T. mentagrophytes. No fungi could be cultured or demonstrated with histological sections of peyers patches. There may have been some fungal products consumed by the rats that accounted for the stimulation of peyers patches.

Antibody and Cell Mediated Immune Responses in the Dermatophyte Infected Germfree-Rat: These results were reported in our last annual progress report breifly:

AMI -- We have observed that germfree rats manifest a poor immunoglobulin response against the invading dermatophyte. A primary and secondary challenge of germfree rats with T. mentagrophytes resulted in an increased level of immunoglobulins in only 1 to 6 bacteria-free animals. Immunoelectrophoresis demonstrated no great increase in gammaglobulins within 70 days after challenge. We were only able to demonstrate 1 out of 6 rats showing a positive precipitin test to purified trichophytin, crude cell wall antigen and soluble cytoplasmic antigen. We are currently assessing the capacity of serum from germfree, T. mentogrophytes monoassociated rats and conventional rats to inhibit T. mentagrophytes. Initial results indicate that serum from the monassociated rats is just as inhibitory as serum from germfree and conventional rats. Further work on these sera indicate that the inhibition of T. mentagrophytes by serum does not appear to be associated with specific immunoglobulin. A student is starting to purify rat serum proteins for further clarification of this serum inhibition of dermatophytes. He will use serum from germfree, monoassociated and conventional rats. We have recently obtained (from Dr. Bazin, Univ. Louvain) myeloma rat tumors that produce specifically IgG, IgM, IgA, or IgE in Louvain rats. We will use these immunoglobulins to quantitate the rats temporal antibody response to a primary dermatophyte infection.

CMI -- In vitro blastogenesis of splenic lymphocytes against phytohemagglutin (PHA) and conconavolin A (ConA) are poor in the dermatophyte infected bacteria-free rats. However, at the same time intervals, the infected rats splenic lymphocytes appear to acquire a good capacity (10 fold) to respond against the T. mentagrophytes antigens we used (crude autoclaved culture extract, formalinized spores, purified T. mentagrophytes antigen from Dr. Kerbs at LAIR). Lymphocyte blastogenesis (at various time periods after infection and clearing of the lesion) indicates to us that clearance of a dermatophyte infection appears to be associated with the acquisition of a CMI response in the rat. It should also be pointed out that the skin testing of conventional rats that have the chronic infection gives a very positive delayed type hypersensitivity reaction with purified T. mentagrophytes antigen, formalinized spores and crude autoclaved antigen. We do not see, however, a typical delayed type hypersensitivity response in the monoassociated germfree rat. A delayed basophil response is very prominent in the conventional rat and this may indicate that a Jones-Mote type of reaction (cutaneous Basophil hypersensitivity) is taking place rather than the typical pure monocyte response as seen in the classic delayed type hypersensitivity response (to PPD) in tuberculin positive individuals.

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Summary of Rat Experiments: This is a good model; a) the primary infection is not as severe as in guinea pigs. The erythema like reaction (with hyphae in skin) clears in the germfree rat in 13-14 days and the hair grows back. The hair does not grow back in conventional rats and a low grade persistent fungal reaction can be seen on the skin for 60-70 days. In conventional rats, there also appears to be a parakeratosis associated with the cleared infected site and it is very similar to psoriasis. The germfree rate does not become overgrown with the dermatophyte (T. mentagrophytes); only T. mentagrophytes caused any obvious dermatophyte-like pathology in the rat model. E. floccosum induced a brown pigmentation (hyperkeratosis) over the inoculated site but no obvious fungal type of lesion. However, the latter pathology (hyperkeratosis) was observed in the skin of male but not female rats. Neither E. floccosum or M. canis survived in the germfree environment. They appeared to die out after each of several challenges of the germfree animal. This may indicate that bacterial associations are needed for the survival of the latter 2 agents on conventional rats.

Our future studies with the rat model will be to begin to find out what has to be done to the immune system of the germfree rat to allow for a more visible and pathologic skin infection by T. mentagrophytes. We will first try neonatal thymectomy. Later studies will include steroid injection, x-ray (LD50 dose), anti-rat lymphocyte serum, or cyclophosphamide suppression.

The latter studies will allow us to begin to study a rat model wherein we can delete selective portions of CMI and/or AMI in order to interfere with host defense mechanisms, and to ascertain how the loss of a specific immune function influences their resistance to dermatophyte infection on the skin.

Nude Mouse Data: The nude mouse is an animal that is congenitally athymic; therefore, it lacks the capacity for the T-cell (CMI) arm of immunity. If dermatophyte infections are controlled by T-cell dependent immunity then the nude mouse should not be able to control dermatophyte infections. We were, however, not able to induce dermatophyte lesions on the skin of nude mice even though skin cultures were positive for T. mentagrophytes 7 days after challenge. Our procedure used a spore inoculum (100,1000, 10,000 spores per occluded site). A similar inoculum took very well on the conventional rat and the guinea pig. Thus either skin bacteria on a microbial flora activation of macrophages (i.e. with lipopolysaccharide or other B-cell mitogens) rendered the nude mouse resistant.

The nude mouse was further evaluated by IV injection of C. albicans. Our studies demonstrated that the nude mouse cleared an I.V. C. albicans challenge better than their littermates (i.e. same strain of mice but with a functional thymus). C. albicans infections are thought to provide classic examples of the importance of T-cell function in host resistance to fungal disease. Our nude mouse data indicates that the importance of T-cell function in immunity to dermatophyte and candida infections is not as clear cut as one would gather from the existing literature. Our initial results on the nude mouse indicate host immune factors (other than CMI) could be operating to control fungal disease (23).

The flora-defined nude mouse did not get obvious dermatophyte lesions. We plan to have germfree nudes in the near future and we will try to infect them with dermatophytes. We have also challenged thymus

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17reconstituted nude mice with C. albicans (I.V.). We found the latter nudes (with proven T-cell function after thymic implants) were just as susceptible to an (I.V.) C. albican challenge as the normal mice. The implanted thymus appeared to suppress immunity to systemic candidiasis that was present in the athymic nude mice. We are going to infect thymus implanted nudes to see if they can also now get a dermatophyte lesion on the skin. Direct macrophage activation might occur in conventional nude mice through lipopolysaccharide (from flora) stimulation or through contact with other B-cell mitogens.

We have now succeeded in decontaminating (with oral antibiotic preparation) an inbred Balb c strain of nude mice. After 9 weeks of oral antibiotics and 2 weeks of withdrawl from the antibiotics we have not seen any microbial outgrowth. This could be the nucleus for our first colony of germfree nude mice (inbred Balb c).

We intend to try to cutaneously infect these germfree nude mice with T. mentagrophytes. Specimens from these nude animals will be used in a joint study with Dr. Hutton at LAIR. He will use scanning, transmission and light microscopy to study the early germination and outgrowth of T. mentagrophytes in the skin. Conventional mice and rats have too much hair that interferes with the scanning and transmission of electron microscopy preparations.

Specific Aims for 1977-1978

1. To continue to develop and define the primary and secondary dermatophyte infection model in germ-free guinea pigs, nude mice and rats.

2. To assess the antibody and cell-mediated immune response to a true, primary and secondary dermatophyte (T. mentagrophytes) infection in germfree guinea pigs, rats and nude mice.

3. To study in conjunction, with investigator at LAIR (Drs. Lancaster, Kerbs, Hutton) the following:
   (a) The skin test response and specificity of germfree and mono-associated guinea pigs to various purified antigen preparations (of T. mentagrophytes) prepared at LAIR.
   (b) The in vitro blatsogenesis response and specificity of germfree and monoassociated guinea pig lymphocytes (spleen, lymph node and peripheral blood) to purified antigen preparations (T. mentagrophytes) prepared at LAIR (Drs. Lancaster and Kerbs).
   (c) To assess whether germfree nude mice can be infected with T. mentagrophytes so that I can supply specimens for the microscopy studies of Dr. Hutton.

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Table I. Stages in the development of gross lesions during primary
          cutaneous _T. mentagrophytes_ infection in guinea pigs

	Days Post-inoculation
ERYTHEMA	5-8
SCALING (24-48 hr)	9-12
SEROUS ULCERATION (24 hr)	11-16
CRUST/SCABS	12-19
SCAR/ALLOPECIA	18-25
HAIR REGROWTH	25-35

8.

TABLE II

Lymphocyte blastogenesis (spleen) during primary

cutaneous infection with T. mentagrophytes

Mean stimulation index (S.I.) ± S.E. (N = 6)

Mitogen/antigen	Day 0	Day 7	Day 14	Day 21
PHA	82 ± 24	32 ± 9.0	7.7 ± 4.0	32 ± 7.6
CONA	211 ± 35	58 ± 18	6.4 ± 2.6	44 ± 9.0
LPS	4.3 ± 1.3	3.5 ± 0.9	1.4 ± 0.3	1.3 ± 0.3
PKW	14 ± 1.3	30 ± 14	3.7 ± 1.8	9.5 ± 4.3
AG I	1.9 ± 0.7	2.4 ± 1.3	1.9 ± 0.4	1.1 ± 0.1
AG II	1.6 ± 0.4	3.0 ± 1.1	2.8 ± 1.3	.98 ± 0.2

TABLE III

Lymphocyte blastogenesis (lymph node) during primary

cutaneous infection with T. mentagrophytes

MEAN STIMULATION INDEX (S.I.) $\pm$ S.E. (N=3)

Mitogen/antigen	Day 0	Day 7	Day 14	Day 21
PHA	432 $\pm$ 195	234 $\pm$ 144	8.0 $\pm$ 6.0	314 $\pm$ 115
CONA	419 $\pm$ 256	411 $\pm$ 149	16 $\pm$ 16	230 $\pm$ 193
LPS	3.6 $\pm$ 0.7	4.1 $\pm$ 1.7	1.3 $\pm$ 0.3	4.6 $\pm$ 1.8
PKW	326 $\pm$ 169	166 $\pm$ 90	6.0 $\pm$ 6.0	211 $\pm$ 9.0
AG I	3.3 $\pm$ 0.9	2.0 $\pm$ 1.1	2.8 $\pm$ 1.2	6.1 $\pm$ 2.0
AG II	1.6 $\pm$ 0.4	1.4 $\pm$ 0.1	1.6 $\pm$ 0.4	14.4 $\pm$ 4.0

Figure 1. The course of primary T. mentagrophytes infection in
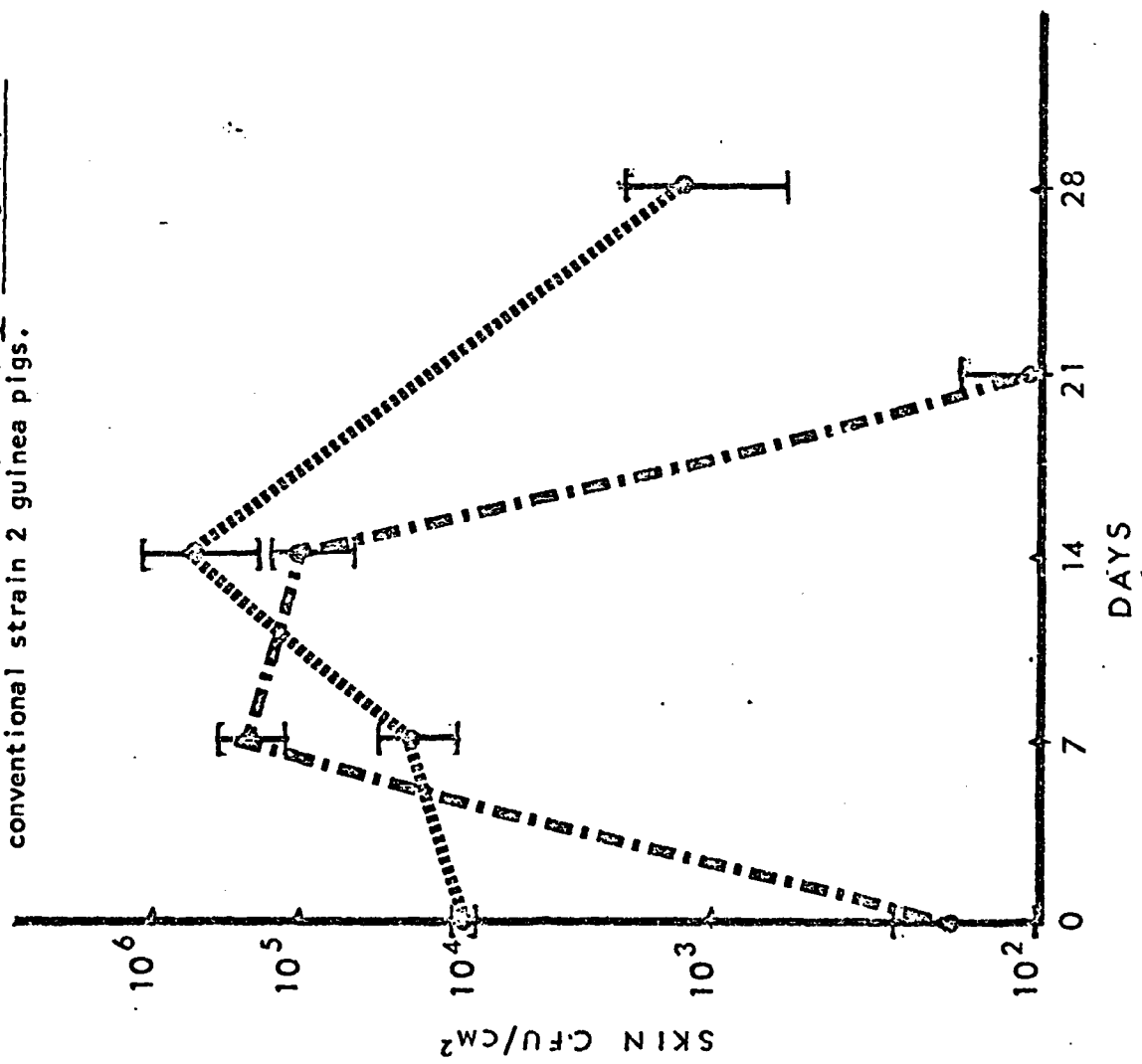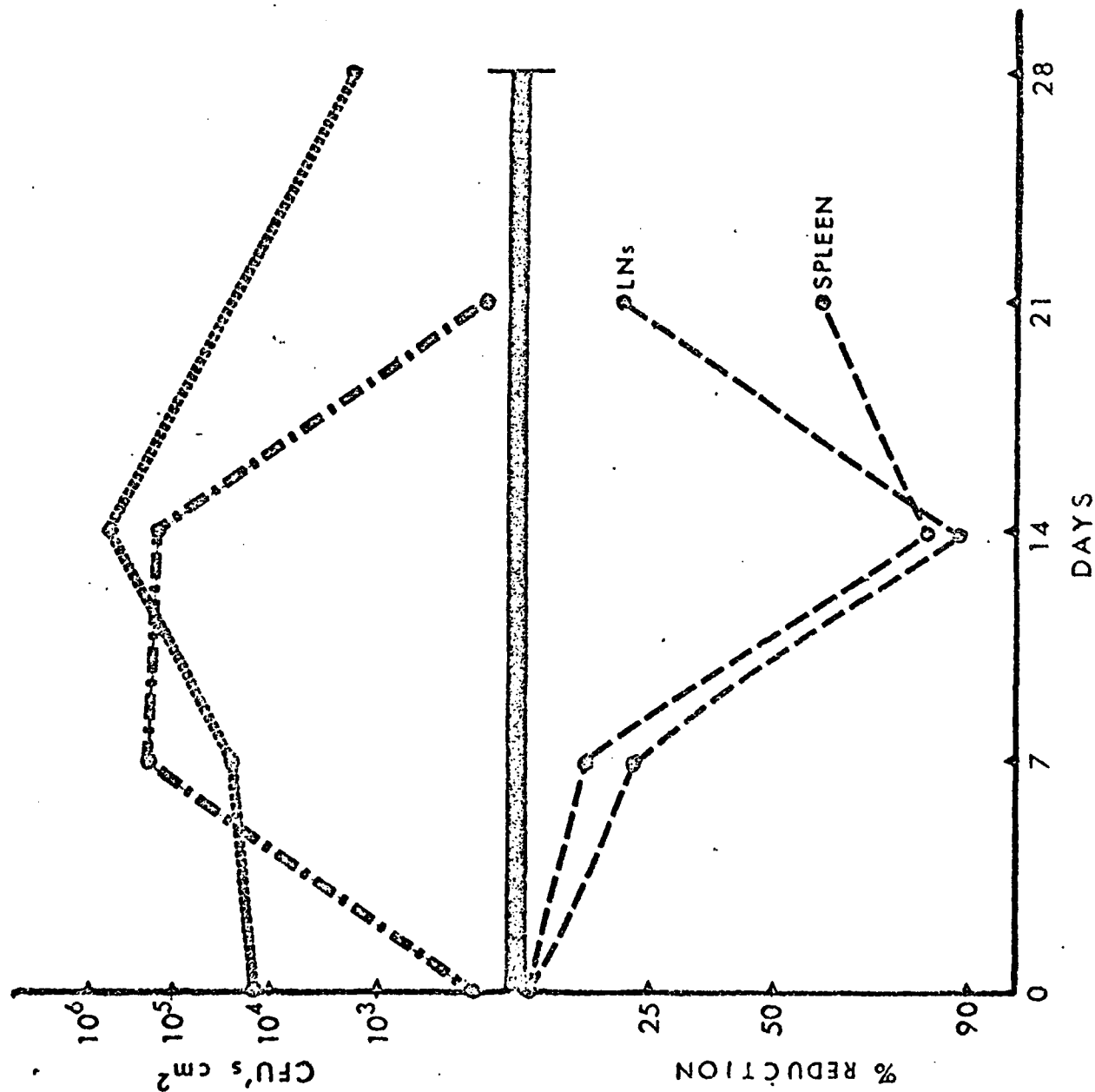conventional strain 2 guinea pigs.

FIGURE 2. Reduction of lymphocyte mitogenic response in vitro during primary T. mentagrophytes infection

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